men with low serum total and non–sex hormone-binding globulin bound testosterone levels (< 350 ng per dl and < 46 ng per dl, respectively) substantially increased lean body mass, reduced urinary hydroxyproline excretion, increased hematocrit, and decreased the total and low-density lipoprotein-cholesterol without changing high-density lipoprotein (HDL)-cholesterol levels.[16] Furthermore, 12 of the 13 men experienced behavioral changes (such as increased libido and feelings of well-being) that permited them to determine correctly whether they were receiving testosterone or placebo, despite the double-blind design of the study. No adverse effects or changes in prostate volume or postvoiding residual urine volumes were noted, but serum prostate-specific antigen levels increased slightly during testosterone treatment.

In a preliminary study, Morley and co-workers found that administering testosterone enanthate, 200 mg every two weeks, for three months to eight elderly hypertensive men with low serum bioavailable testosterone levels (<70 ng per dl) substantially increased hand-grip strength, serum osteocalcin levels, and hematocrit and decreased total cholesterol without changing HDL-cholesterol levels, compared with six untreated control subjects.[17]

Despite the short-term nature of these studies, testosterone treatment of mildly androgen-deficient elderly men had notable beneficial effects on lean body mass, muscle, and hematocrit and possibly on bone turnover and mood. No significant adverse clinical effects were noted.

As discussed by Swerdloff and Wang, when contemplating the use of testosterone replacement therapy in elderly men with mild androgen deficiency, the possible risks as well as benefits must be considered.[15] Of particular concern is the potential for testosterone treatment to stimulate benign or malignant prostate growth—benign prostatic hyperplasia and prostate carcinoma, respectively—and to reduce HDL-cholesterol levels that may result in an increased risk of coronary artery disease.

Larger and longer term studies are needed to determine both the risks and benefits of androgen replacement therapy in elderly men. To avoid the adverse effects of pharmacologic levels of androgens, a reasonable initial goal of therapy in elderly men is to restore normal testosterone levels. If the late evening to morning rise in serum testosterone levels is found to be physiologically important (for example, in maintaining normal sleep quality), it may also be useful to restore a normal circadian variation of serum testosterone levels. Such truly physiologic testosterone replacement is now possible and practical using recently developed transdermal testosterone delivery systems.[18] Recent evidence suggests an important role for dihydrotestosterone in stimulating benign prostatic hyperplasia. Because of concerns regarding the stimulation of prostate growth and the suppression of HDL levels during testosterone therapy, it may be useful to explore combining testosterone with a 5α-reductase inhibitor or to use an androgen preparation, such as 7α-methyl-19-nortestosterone that is aromatized but not 5α-reduced.[19]

In summary, aging in men is associated with a gradual and progressive decrease in serum testosterone levels and a decline in various physiologic functions. The physiologic importance of lower androgen levels in elderly men and their relationship to age-related decreases in sexual interest and function, muscle mass and strength, and bone mass and alterations in mood and sleep quality remain unclear. Clarification of the functional significance of reduced testosterone levels with aging ("andropause") awaits carefully designed, long-term, placebo-controlled trials to determine the possible risks and benefits of androgen replacement therapy in selected elderly men.

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Lessons From Hypersensitivity Pneumonitis

THE RESPIRATORY TRACT is one of three sites of interaction of humans with the environment (the other two being the skin and gastrointestinal tract). The 7,200 liters of air

inhaled daily by normal adults contains many substances that may injure the body. The inhalation of potentially toxic substances is usually followed by the removal or detoxification of these substances without injury to the person. This beneficial effect is achieved by various mechanical means—mucociliary escalator, cough, sneeze—and by detoxification by cells or cell products. Usually the immune consequences of inhaling antigens favor the detoxification and neutralization of foreign material—macrophages are activated, polymorphonuclear leukocytes and perhaps eosinophils are recruited, lymphocytes are sensitized—and are favorable to the host. At times, however, the immune consequences are themselves injurious, such as with asthma, allergic rhinitis, and hypersensitivity pneumonitis. Reasons for the occurrence of adverse effects in some healthy persons are diverse, but likely include differences of inherent characteristics. As an example, atopic asthma and allergic rhinitis are related to a genetic predisposition to form immunoglobulin (Ig) E antibodies following respiratory tract exposure to common aeroallergens.

Hypersensitivity pneumonitis, also known as allergic alveolitis, is a group of uncommon interstitial pulmonary diseases that offer important insights into the immunopathogenesis of more frequently encountered pulmonary disorders. The most common examples are farmer's lung disease and avian-associated hypersensitivity pneumonitis (such as pigeon breeder's disease and bird fancier's disease). As discussed by Kaltreider elsewhere in this issue,[1] the acute response to inhaling materials capable of causing hypersensitivity pneumonitis exhibits features of immune complex mediation, and the chronic disorder displays features of delayed-type hypersensitivity. Hypersensitivity pneumonitis represents the pulmonary diseases most clearly associated with immunologic events caused by inhaling known antigens. Clarification of the immune mechanisms of hypersensitivity pneumonitis may aid in devising innovative and more effective interventions in more common pulmonary diseases.

Several lessons are to be learned from hypersensitivity pneumonitis:

- The history remains the basis of diagnosis.
- Many lung diseases are immunologically mediated.
- Cells associated with delayed-type hypersensitivity are important determinants of immunoglobulin production, especially IgE.

Acute hypersensitivity pneumonitis presents as fever, dyspnea, hypoxemia, and radiologic changes of diffuse pulmonary interstitial nodules. This constellation of signs and symptoms is nonspecific, and the illness is often diagnosed as infectious pneumonia. Only a history of exposure to a particular environment four to six hours before the onset of symptoms, coupled with a past occurrence of similar episodes after the same exposure, allow the diagnosis to be considered. The presence of serum antibodies to the causative agent confirms previous sensitization. Lung biopsy is seldom necessary, but, when done, the specimen has characteristic pulmonary histologic features of chronic interstitial inflammation, often with poorly formed granulomata or bronchiolitis.

The chronic syndrome is more difficult to diagnose. The clinical presentation is that of pulmonary interstitial fibrosis with dyspnea and weight loss. Persistent questioning of the patient will disclose long-standing low-level exposure to likely agents. Serum antibody levels confirm exposure and sensitization. Avian antigens, especially in domestic situations, are most commonly involved.[2]

The acute response to the inhalation of offending material is characterized by neutrophilia found in bronchoalveolar lavage (BAL) fluid,[3] followed by interstitial granulomatous inflammation and $CD8^+$ lymphocytosis in the BAL specimen. Bronchoalveolar lavage lymphocytosis reflects exposure to offending material and may not be associated with evident pulmonary disease.[4] The presence of BAL $CD8^+$ lymphocytosis, although common, is dependent on the type of hypersensitivity pneumonitis and time since the last exposure.[5]

High-resolution computed tomographic scans of the chest show centrilobular nodules, ground-glass radiodensities, and emphysema. Hypersensitivity pneumonitis can be distinguished from sarcoidosis because nodules tend to be bronchocentric in hypersensitivity pneumonitis and follow bronchovascular bundles in sarcoidosis.

The treatment of acute disease with parenteral glucocorticosteroids accelerates the return of pulmonary function tests and gas exchange towards normal, but compared with untreated patients, does not alter pulmonary function at three months from the onset.[6]

These diseases carry substantial morbidity and mortality. Acute severe hypersensitivity pneumonitis rarely results in death. Long-term exposure more commonly results in progressive pulmonary fibrosis. A recent report from Mexico City describes a 30% mortality over five years in patients with pigeon breeder's disease.[2]

An unanswered question is the frequency of undiagnosed hypersensitivity pneumonitis in patients presenting with pulmonary interstitial fibrosis. Fully 10% of patients referred to the National Jewish Center in Denver, Colorado, with the diagnosis of interstitial fibrosis had pulmonary histologic features suggestive of hypersensitivity pneumonitis and usually a history of exposure to birds (T. King, MD, oral communication, July 1993). This emphasizes the necessity of obtaining a careful history, especially in patients with previous exposure to avian antigens.

Many pulmonary diseases, such as sarcoidosis and interstitial fibrosis, have features of immunologic reactivity that imply an immune pathogenesis, but in which the inciting antigen(s) has not been identified. Understanding the immunologic reactions that occur after the inhalation of known antigens would aid in the search for evidence of similar reactions in other pulmonary diseases with possibly similar mechanisms. Ultimately, the goal is the interruption of these immunologic reactions to ameliorate or prevent lung damage.

Although acute and chronic responses to antigen inhalation often occur in the same persons, they differ considerably and may represent two different responses to toxic material. The acute response apparently occurs in all persons with exposure to large amounts of antigen and is not associated with evidence of previous sensitization (serum antibody not present). In the case of farmers exposed to hay, this response has been called organic dust toxic syndrome. It is apparently more common than classic hypersensitivity pneumonitis in farming populations with exposure to the agents that cause farmer's lung disease and is characterized by transient fever, dyspnea, nonproductive cough, peripheral blood leukocytosis, and BAL neutrophilia. Unlike hypersensitivity pneumonitis, organic dust toxic syndrome is not associated with chest radiographic changes or permanent lung damage[7] and may represent immune complex-mediated lung injury as described by Kaltreider.[1] The distinction between acute hypersensitivity pneumonitis and organic dust toxic syndrome is not obvious, and it is possible that the former represents a recurrence of the latter in a person with previous exposure to antigen.

Unlike virtually all other pulmonary diseases, both hypersensitivity pneumonitis and organic dust toxic syndrome are more common in nonsmokers than in smokers. Cigarette smoking has many effects on the lung, and long-term cigarette smokers display some features of immune suppression. It is not clear which of the many effects of cigarette smoking lead to the observed protection against hypersensitivity pneumonitis.

Current concepts of delayed-type hypersensitivity suggest a key role for the T_H1 subset of $CD4^+$ cells in hypersensitivity pneumonitis. The expression of delayed-type hypersensitivity and of humoral immunity is a reflection of the activity of subtypes of $CD4^+$ T cells. T cells include $CD4^+$ (helper) and $CD8^+$ (suppressor or cytotoxic) subsets. $CD4^+$ cells can be divided into T_H1, T_H2, or T_H0 subsets by their patterns of cytokine secretion. T_H1 cells preferentially secrete interleukin (IL)-2, interferon gamma, and tumor necrosis factor-β, activate macrophages, and are responsible for delayed-type hypersensitivity reactions. In general, T_H1 cells do not provide help for immunoglobulin production. T_H2 $CD4^+$ cells secrete IL-4, IL-5, IL-10, and IL-13; provide help for immunoglobulin (particularly IgE) secretion; enhance eosinophil production, survival, and activity; and promote mast-cell maturation and proliferation. The development of either a predominant T_H1 or T_H2 response is dependent on many factors, including attributes of the antigen, the site of delivery, the adjuvant used, and the type of antigen-presenting cell encountered. Interestingly, cytokines secreted by one $CD4^+$ subset inhibit the development of the reciprocal subset. T_H0 cells secrete a mix of cytokines characteristic of both T_H1 and T_H2 cells.[8] Recent evidence from studies of animals indicates that $CD4^+$ cells can adoptively transfer experimental hypersensitivity pneumonitis.[9] The responsible cells have not yet been classified as T_H1, T_H2, or T_H0.

There is increasing evidence that common lung diseases once thought to be mediated by IgE or nonimmune mechanisms show delayed-type hypersensitivity. Asthma can be described as a chronic eosinophilic bronchitis of unknown cause associated with prominent changes of bronchial mucosal T-cell number, state of $CD4^+$ activation, and cytokine secretion. Asthma has many of the features of delayed-type hypersensitivity, such as the activation of bronchial mucosal lymphocytes and eosinophils.[10] Cytokines or messenger RNA for cytokines associated with delayed-type hypersensitivity reactivity, such as tumor necrosis factor-α, granulocyte-macrophage colony-stimulating factor, IL-1, IL-2, and IL-6, are present in BAL and in bronchial mucosal cells.[11]

Other common features of atopy—eosinophilia, mast cell hyperplasia, and increased levels of IgE—are indicative of T_H2 $CD4^+$ cell activity. Current research activity is directed toward deciphering the precise interrelations of T_H1, T_H2, and T_H0 $CD4^+$ cells in asthma.

The examination of hypersensitivity pneumonitis offers clinical insights into the diagnosis and immunopathogenesis of more common pulmonary diseases and illustrates current concepts of immune regulation.

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